REMARKS/ARGUMENTS

The present application previously included claims 46-188, and was the subject of both a restriction requirement and an election of species. Claims 90-188 were previously restricted out of the application, and those claims have been cancelled by this amendment. Elected claims 46-89 have been examined, based on the species Pluronic F68 as the surfactant. Claims 72-74 have been allowed. Claims 46-71 and 75-89 have been rejected under §103, and Applicant hereby responds to the stated rejections.

Claims 65-71 and 81 have been cancelled. Claims 75-80, 82-86, and 88-89 have been amended to depend from allowed claim 72, and claim 87 therefore now depends indirectly on claim 72, and these claims are therefore submitted to be allowable. New claims 189-197 also depend directly or indirectly from claim 72 and are submitted to be allowable on that basis.

Claims 46-64 also remain pending. Applicant submits that claim 46, and claims dependent therefrom, are patentable over the cited art for reasons set forth hereafter.

Applicant further requests consideration of the non-elected species in view of the allowability of the claims in the case.

Claims 46-50, 57-60 and 63-64 have been rejected under §103(a) as being unpatentable over Skrabanja et al. (USPN 5,929,028) in view of Koll et al. (USPN 6,346,274). The Office Action proposes that it would have been obvious to interchange a surfactant from Koll with a surfactant disclosed in Skrabanja to arrive at the present invention, and Applicant respectfully disagrees for reasons set forth herein.

Applicant understands the Examiner's position, in brief, to be that Skrabanja teaches the use of Tween 20 with FSH, and that Koll suggests that Pluronic 68 can be substituted for Tween 20. Applicant respectfully disagrees for several reasons. Applicant submits that Koll at best says nothing about the potential use of Pluronic 68 with FSH, and if anything it

teaches away from the present invention. Applicant further submits that Skrabanja and Koll address completely different issues and would not be combined in the manner suggested.

As a preliminary, Applicant notes the Examiner's characterization of the comments by Applicant in the previous amendment, and wishes to clarify the record, and to ensure that there is no misunderstanding as to Applicant's positions regarding the cited art. Applicant did not "admit", and does not agree, that "Tween 20 and Pluronic F68 induce similar effects in preventing aggregation of proteins such as EPO or FSH". (July 20, 2007 Office Action, page 3) Applicant's comments were as follows:

> "Pluronic F68 is only mentioned once in Koll, namely in Table 1 in a very specific combination with EPO. Table 1 simply presents that the use of Pluronic F68, and numerous other additives, with ABA triblock copolymer microparticles containing EPO resulted in a reduction in the aggregation of the microparticles. Tween 20 and Pluronic F127, at the same w/w % level, provided a similar reduction in aggregation of the ABA microparticles. Thus, a person skilled in the art would not even know from Koll whether Pluronic F68 had any advantageous effects over Tween 20 or Pluronic F127 with respect to the specific combination of EPO on ABA microparticles. It certainly is impossible to conclude from Koll whether Pluronic F68 would be an appropriate surfactant for any other peptide such as FSH." (Amendment in Response to the November 1, 2006 Office Action, pages 26-27)

As this passage indicates, the proper characterization of Koll is that it only mentions Pluronic F68 "in the specific combination of EPO on ABA microparticles." In that specific combination, the presence of Tween 20, Pluronic F68 and several other surfactants lowered aggregation. Applicant further noted that Koll would not teach whether Pluronic F68 would be an appropriate surfactant for FSH, as further explained hereafter.

Koll does not even suggest the interchangeability of surfactants for a given protein. As shown in Table 1, for the single combination of EPO in ABA particles, in comparison to Tween 20, 7 additives functioned better to lower aggregation, compared to 6 that worked as well and 2 that had no effect. Comparing Tables 1 and 2, it is shown that even the change of microparticle for the same EPO can change the efficacy of a surfactant. For the EPO/PLGA

microparticles of Table 2, bovine serum albumin (5% and 10%) was less effective, arginine worked the same, and Pluronic F127 went from lowering to increasing aggregation.

Based on the limited examples available from a comparison of Tables 1 and 2, it is only suggested, if anything, that there is no predictability for how different surfactants will work for a given protein. The Examiner proposes that a comparison of the two Tables would motivate a person of skill in the art to use Pluronic F68 or Tween 20 because Pluronic F127 did not work for EPO in PLGA particles. There simply is insufficient data in the two Tables to provide such a motivation. For example, there is no similar comparison as to the use of Tween 20 or Pluronic F68 for EPO in both the ABA particles of Table 1 and the PLGA particles of Table 2. Applicant submits that the Examiner's argument is the result of hindsight stemming from knowledge of the present invention. Moreover, the Tables are related to EPO, not FSH, and therefore do not teach anything as to how the listed surfactants would work for FSH.

At the outset, Applicant disputes the argument that a person of ordinary skill in the art would combine the Skrabanja and Koll references in the manner suggested in the Office Action. First, Koll is limited to the effect of Pluronic F68 and other surfactants. for reducing aggregation of polypeptides that are encapsulated in a block copolymer. Skrabanja is not directed to microparticles and the effect of surfactants with FSH contained in such particles, while the entire focus of Koll is formulations which address specifically the properties associated with microparticles.

Moreover, Skrabanja and Koll are focused on different problems. Skrabanja discloses the use of surfactants as "anti-adsorption agents" to prevent "adsorption of the protein to the walls of the container". Column 5, lines 15-40. Koll, on the other hand, is focused on reducing aggregation. These are clearly separate problems, associated with different causes. The Office Action suggests that one would have been motivated to substitute the Pluronic

F68 of Koll for the Tween 20 of Skrabanja in order to "preclude both the aggregation of FSH . . . and . . . the loss of FSH by adsorption to vessel surfaces". Office Action of July 20, 2007, page 6. However, the result from substituting Pluronic F68 for Tween 20, based on the disclosures, would eliminate the reduction of adsorption of FSH, which would defeat the purpose of the Skrabanja teachings. Put another way, it would not be obvious to modify the Skrabanja formulations, which prefer the inclusion of Tween 20 to reduce adsorption of FSH, with any of the surfactants in Koll, since they are identified as useful for reducing aggregation, a different phenomena.

Contrary to the Office Action, the Skrabanja reference does not state at column 2, lines 20-25, that both aggregation and adsorption are recognized as problems in the pharmaceutical industry. Office Action of July 20, 2007, page 6. It simply indicates that "The stability of proteins in aqueous formulations is generally a problem in pharmaceutical industry."

Finally, Applicant notes that the Office Action greatly over-simplifies the content of both Skrabanja and Koll, which distorts a fair consideration of what the references would teach or suggest to a person of ordinary skill in the art. As the Examiner indicates, a prior art reference may be relied upon for what it "would have reasonably suggested". While it may be true that the "mere disclosure of more than one alternative" does not constitute a teaching away from any one alternative, that does not mean that a reference "reasonably" suggests each of millions of possible combinations of disclosed elements.

Contrary to the simplifications set out in the Office Action, the teachings of Skrabanja and Koll are so all-encompassing that they do not fairly teach specific combinations, let alone substitutions from one to the other. The Office Action indicates that "Koll discloses microparticles composed of encapsulated FSH in presence of Pluronic F68 or Tween 20. In fact, the combinations of the polypeptides (bridging columns 4-5 of Koll) and of the

"pharmaceutical additives" (e.g., column 8, lines 4-11 and Tables 1 and 2 of Koll) do not direct one to "FSH in presence of Pluronic F68 or Tween 20". There are 34 classes of polypeptides listed encompassing thousands of individual compounds, and 8 categories of pharmaceutical additives also encompassing hundreds or thousands of compounds. The combination of encapsulated FSH in the presence of Pluronic F68 is not specifically disclosed, and it is but one of perhaps millions of combinations which could be assembled based on the Koll text.

Similarly, the examiner refers to Koll as preferring polypeptides such as "EPO, calcitonin, FSH etc.", citing to column 5, lines 5-10 and to claim 6. Office Action of July 20, 2007, page 5. These are not indicated as preferred embodiments in the text, but are simply referred to as polypeptides "which come into consideration within the sense of the invention" and which are "mentioned as examples." Koll, column 4, line 51 to column 5, line 9. Further, as previously noted, Koll does not point to these three polypeptides, but rather lists these among 34 classes of polypeptides, of which only EPO is the focus of subsequent descriptions and of the examples.

The Skrabanja patent discloses liquid gonadotropin-containing formulations characterized in that the formulation comprises stabilizing amounts of (a) a polycarboxylic acid or a salt thereof and (b) a thioether compound. Skrabanja mentions the optional inclusion of one or more nonionic surfactants such as Polysorbate 20, NF (Tween 20), Polysorbate 80, NF (Tween 80), Brij 35, and Pluronic F123. Skrabanja does not disclose any of the pluronic surfactants claimed in the present application, namely F68, F77, F87 or F88.

The Koll patent discloses microparticles containing polypeptides for parenteral administration. The microparticles comprise an ABA triblock copolymer, and are intended thereby to keep the aggregation of the active substance as low as possible. Koll mentions FSH as a possible active ingredient in a very long list spanning from column 4, line 51 to

column 5, line 9. The peptide erythropoietin (EPO) is clearly the preferred target of the Koll patent, and is the only subject of the several described Examples.

Moreover, the focus of the Koll patent is on the preparation of microparticles containing an ABA triblock copolymer, with which a large, laundry list of additives may be included. This listing includes serum proteins, polyamino acids, cyclodextrins, cyclodextrin derivatives, saccharides, amino sugars, amino acids, detergents or carboxylic acids, as well as mixtures of these additives. See the Abstract, lines 8-12, and column 8, lines 4-11. Given this long and diverse listing, and the single additive EPO described in the Examples, the Koll patent cannot fairly be said to teach specific combinations of the multitude of additives mentioned therein. More specifically, Koll cannot be said to teach the combination of Pluronic 68 (or Pluronic F77, Pluronic F87 or Pluronic F88) specifically with FSH or a variant thereof. Koll discloses a wealth of excipients that may be optionally used, and in that context mentions also detergents such as Tween 20, Tween 80 and pluronics as a class. But the general description does not contain any teaching as to which detergent/surfactant to choose for which peptide, and it is silent on Pluonic F68.

It is therefore submitted that the skilled person would not have had an incentive to replace Tween 20 in Skrabanja with Pluronic F68 (or Pluronic F77, Pluronic F87 or Pluronic F88) in view of Koll. EPO is a compound which is completely unrelated to gonadotropins such as FSH. EPO is a monomeric protein whereas FSH is a dimeric protein and thus particularly unstable and sensitive to destabilizing effects/additives. In contrast to monomers, dimers may dissociate and therefore have per se a higher chance to be susceptible to destabilizing effects of additives. Experimental results with monomeric proteins such as EPO may not be simply extrapolated to dimeric proteins such as FSH. The skilled person knows that surfactants may have very different effects depending on the active ingredients with

which they are combined and this is even more the case if the active ingredients have so different structures as EPO and FSH.

Claims 54-56 and 61-62 cover inventive compositions which further include phenol or m-cresol as bacteriostatic agents. As indicated in the specification, the use of Pluronic F68 (or F77, F87 or F88) solves a problem of precipitation which occurs with certain other surfactants. Specifically, these claimed surfactants "obtain a stable formulasion that avoids the problem of precipitation in the presence of a bacteriostatic agent, such as m-cresol and phenol. Precipitation, resulting in the formation of turbid or milky solutions occurs when TWEEN 20 is used with m-cresol or phenol." Page 12, lines 28-35. As stated in Example 1:

> "From visual examination of the formulations, it was determined that TWEEN 20 cannot be used with m-cresol and phenol because FSH formulations containing TWEEN 20 and m-cresol or TWEEN 20 and phenol presented a white opalescent suspension. In contrast, FSH formulations containing Pluronic F68 did not exhibit this problem with m-cresol and phenol. The use of Pluronic F68 permits the use of phenol and m-cresol."

Applicant submits that this is an unobvious advantage for Pluronic F68 in the formulations including m-cresol or phenol, and that those claims are therefore patentable over the cited art for this additional reason.

Reconsideration of the above-identified patent application, as amended and in view of the foregoing remarks, is respectfully submitted. An action on the merits and allowance of the claims is solicited. If the Examiner believes that it would expedite examination of this case, the Examiner is requested to contact the undersigned directly.

Respectfully submitted,

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